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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,086	10/24/2001	Avi J. Ashkenazi	GNE.2630P1C64	4093

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,086	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 58-77 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 58-77 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/30/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 58-77 are pending in the instant application. Claims 1-57 have been canceled and claims 58-77 have been added as requested by Applicant in the Preliminary Amendment filed October 24, 2001.

Specification

2. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. See page 124, line 37, page 127, line 18, page 233, line 1, page 175, line 1, page 276, line 1, page 309, line 32, page 311, line 33, page 313, lines 5, 6, 20 and 23, at least. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Double Patenting

3. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application.

A sequence search of the pending and published application databases has revealed that there are a series of applications in which SEQ ID NO: 6 is present but that do not claim the polynucleotide. However, there is at least one other application filed by the applicants which contains the polynucleotid of SEQ ID NO: 15 which is identical to the polypeptide of SEQ ID

NO: 6, and which may contain possible conflicting claims. Due to the large number of applications that contain this sequence, the examiner is unable to determine if any of these applications have claims directed to this polynucleotide. Applicant is required to point out to the Examiner all double patenting issues. See MPEP § 1.105.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained will be accepted as a complete reply to the requirement for that item.
This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Formal Matters

4. The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R."1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 209786 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, pages 372-374).

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 58-77 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 58-77 are directed to the nucleic acid of SEQ ID NO: 6 encoding the protein of SEQ ID NO: 7, identified as PRO274. The instant specification discloses that PRO274 is a 492 amino acid protein, and is presumably a membrane-bound protein with extracellular domain from amino acids 1-85, and transmembrane domains from amino acids 86-106, 163-179, 191-205, 237-253, 327-343, 357-374, 408-423 and 431-445 (Fig. 4). The specification teaches that PRO274 has homology to the 7-transmembrane receptor family and to FN54 protein. However, the protein (or encoding nucleic acids) do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The claims are directed to isolated nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity to a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 7, with or without its signal peptide, or to the extracellular domain of SEQ ID NO: 7 with or without its signal peptide. Dependent claims are directed to vectors and host cells comprising the isolated nucleic acids. The specification contains numerous asserted utilities for the polypeptide and encoding nucleic acid at pages 190-199, including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify

molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO274 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO274.

The specification teaches that PRO274 has (unspecified) homology to the 7-transmembrane receptor family. The amino acid sequence of the putative PRO274 peptide is shown in Figure 4 of the specification, in which transmembrane domains are identified, however there is no disclosure that the protein is expected to be a transmembrane protein other than identification of putative transmembrane domains. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO274. Without any information as to the specific properties of PRO274, the mere identification of such as having significant sequence homology to the 7-transmembrane receptor family and/or FN54 protein (which has no disclosed activity) sufficient to impart any particular utility to the claimed polypeptides or encoding nucleic acids.

The specification at pages 331-346 describes experiments in which PRO274 encoding genes are asserted to be amplified in the genome of certain human lung primary tumors. At pages 119-137 it is disclosed that nucleic acids encoding PRO274 had ΔCt values of at 1.24, 1.00 and 1.61 for 3 primary lung tumors, LT4, LT16 and LT18, respectively, for which a value of

1.00 corresponds an amplification of two-fold over normal tissue. From Table 8 on page 338, PRO274 was amplified in one (LT4) out of nine human lung tumor adenocarcinoma tumors, and was amplified in two (LT16 and LT18) out of nine human lung tumor squamous cell carcinomas. Given that PRO274 was amplified in only a very small number of tumors of the same type, the data do not support the implicit conclusion of the specification that PRO274 shows a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnostic of such. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Even if the data were corrected for aneuploidy, one of ordinary skill in the art would not conclude that PRO274 would be diagnostic for lung cancer, due to the lack of overexpression in the majority of primary tumor types.

Even *if* the data demonstrated a increase in copy number of PRO274 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Also, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the protein would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95:14717-14722) teach that

> "An analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was

> significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See page 14722, second paragraph of left-hand column; pp.14720-14721; Pages 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors".

Gygi et al. (Molecular and Cellular Biology, March 1999, p. 1720-1730), studied over 150 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Gygi et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (abstract and Figure 5).

Thus, the data do not support the implicit assertion that nucleic acids of PRO274 or the encoded polypeptide can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO274 is overexpressed in any cancer to the extent that the nucleic acids or polypeptides could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 58-77 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Even if the specification were enabling of how to use

the PRO274 nucleic acids, enablement would not be found commensurate in scope with the claims. If one of skill in the art does not know how to use the nucleic acids or proteins the skilled artisan would clearly not know how to use nucleic acid molecules that are 80-99% identical to a nucleotide sequence encoding the polypeptide of SEQ ID NO: 50 or nucleic acids that hybridize to a nucleotide sequence encoding the polypeptide.

6.2 Claims 58-62 and 71-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of

distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 7, with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35

U.S.C. § 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 71-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 71-73 are indefinite because they encompass a nucleic acid molecule which hybridizes to the nucleic acid of SEQ ID NO: 6 or a nucleic acid encoding a polypeptide of SEQ ID NO: 7, which may be under "**stringent**" conditions. Though the specification on page 129 describes various hybridization and wash conditions, they are exemplary, and stringent conditions may be low, moderate or high. The claims are considered indefinite, because the metes and bounds of the patent protection desired are not clearly set forth.

Priority Determination

35 U.S.C. § 120 states that:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

8. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because the instant application does not meet the requirements of 35 U.S.C. § 112, first paragraph, for those reasons given above and it is a continuation of the applications listed in the priority map filed June 21, 2002, the prior applications do not meet those requirements and, therefore, are unavailable under 35 U.S.C. § 120 or § 119(e). The effective priority date of the instant application is considered to be the filing date of this application, October 24, 2001, because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

Rejections over Prior Art

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 58-67 and 71-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270.

Claims 58-67 and 71-76 are drawn to nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity, respectively, with a nucleic acid encoding the protein of SEQ ID NO: 7, or nucleic acids that hybridize to nucleic acid of SEQ ID NO: 6 under stringent conditions and are at least 10 nucleotides in length. Claims 74-76 encompass vector and host cell of claim 58.

Ho et al. disclose mouse and human ANK protein and encoding nucleic acids, the human protein of which is 100% identical to the protein of SEQ ID NO: 7 of the instant application (Fig. 3A and attached sequence alignment), vector comprising the encoding nucleic acids and host COS-7 monkey kidney host cells. The nucleic acid sequence of Ho et al. is 99.7% identical to nucleotides 1-2943 of SEQ ID NO: 6 of the instant invention, and therefore the nucleic acid of Ho et al. would hybridize under stringent conditions to the nucleic acid of SEQ ID NO: 6. Although Ho et al. is silent with respect to the nucleic acid being operably linked to control sequences recognized by a host cell transformed with the vector, because the protein was expressed and purified from the host cell, the nucleic acid was by necessity operably linked to control sequences. Therefore, Ho et al. anticipates the claims.

Claims 68-70 are not included in the rejection, because the sequence of Ho et al. differs from SEQ ID NO: 6 of the instant application by 4 mismatches, one of which is in the coding region (nucleotide 376).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 77 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al., Science, Vol. 289, July 14, 2000, pages 265-270, in view of Ni et al., U.S. Patent No. 5,977,309, Nov. 2, 1999.

Claims 77 encompasses a host cell which is a CHO, *E coli* or yeast cell.

The teachings of Ho et al. are discussed above. Ho et al. does not teach that the host cell could be a CHO , *E coli* or yeast cell.

At column 8, lines 46-54, Ni et al. discuss a number of host cells that are appropriate for cloning and expression:

> "As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as E. coli, Streptomyces, Salmonella typhimurium; fungal cells, such as yeast; insect cells such as Drosophila S2 and Spodoptera Sf9; animal cells such as CHO, COS or Bowes melanoma; adenoviruses; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein."

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use as host cells either CHO, *E coli* or yeast, since Ni et al. teach that these, among a number of other host cells, would be appropriate for use in cloning and expression. The motivation and expectation of success are both taught by Ni et al. who teach that these host cells are generally useful for such.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, se **http://pair-direct.ispto.gov.** Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner